

Early Non-White Matter Changes in Cerebrovascular Integrity in Mouse Brain Following Bilateral Carotid Artery StenosisJill Roberts, PhD¹ • Michael Maniskas, PhD¹ • Gregory Bix, MD, PhD¹**3a**¹*Sanders-Brown Center on Aging, University of Kentucky*

Bilateral carotid artery stenosis (BCAS) is an experimental model of vascular dementia which leads to white matter lesions and cognitive dysfunction in mice. Unfortunately, with time the white matter pathology worsens and spreads to the hippocampus and cortex. While some variability in the temporal and spatial distribution of brain injury may result from inter-mouse strain differences in cerebrovascular anatomy, coil size employed to constrict the carotids and surgical technique, it is generally accepted that hippocampal, striatal and cortical pathology is not significantly present prior to 30 days. However, as changes in cerebrovascular integrity, i.e. blood-brain barrier (BBB) permeability, are known to precede more overt brain pathology in stroke, we hypothesized that BBB changes could occur earlier after BCAS in the hippocampus, striatum and cortex and be a precursor of longer term pathology in these regions. In our study, 3 month old male C57/Bl6 mice underwent BCAS with 0.18 mm coils or sham surgery control and cerebrovascular integrity was analyzed by collagen IV (vascular basement membrane component), tomato-lectin (marker of endothelial cells) and Ki-67 (marker of cell proliferation) immunohistochemistry after 7, 14, or 21 days (n=4 animals per group per day). By day 14 we noted that collagen IV staining density was significantly less in the hippocampus compared to sham controls. Surprisingly, both collagen IV and tomato-lectin staining pattern indicate blood vessel disruption in not only the hippocampus but the striatum as well. Expression of Ki-67 increased in both of these regions, and further co-labeling studies will shed light on cell specificity. Similar differences were noted at all days tested, with few changes observed in the cortex. In conclusion, this study demonstrates for the first time that changes in cerebrovascular integrity occur earlier than expected after BCAS and suggests that such changes might underlie the gradual development of BCAS non-white matter pathology.